In re Application of: Pietrokovski et al
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Examiner: Ogunbiyi
Group Art Unit: 1645
Attorney Docket: 29489

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-121 are in this Application. Claims 19-121 have been withdrawn from consideration. Claims 1-18 have been rejected. Claims 2-4 have been canceled herewith. Claims 1, 5-6, 11, 13, 14, 16 and 17 have been amended herewith.

35 U.S.C. § 112, First Paragraph Rejections

The Examiner has rejected claims 1-18 under 35 U.S.C. 112 First paragraph, because the specification while being enabling for a chimeric polypeptide comprising an autoprocessing segment placed between two polypeptide segments does not reasonably provide enablement for the invention as claimed.

Applicant strongly disagrees with this statement and directs the Examiner's attention to the Examples section which clearly show that the auto-processing segment of the present invention is capable of independent cleavage at both the C- and N-terminii as well as coordinated cleavage at both domains and auto-splicing of flanking sequences.

The experimental results presented in the Examples section of the instant application clearly state that:

> "protein products generated following *in-vitro* transcription/translation of the MBP-PsyBIL-CBD expression construct pC2C-PsyBIL displayed molecular weights corresponding to the uncleaved precursor MBP-PsyBIL-CBD, the splicing product MBP-CBD, and the carboxy terminal cleavage product MBP-PsyBIL. (emphasis added)

Thus, the splicing domain of the present invention is capable of mediating splicing of flanking amino acid sequence, showing both N- and C- terminal cleavage capabilities, as well as being capable of some independent auto-cleavage at a C-terminus thereof when flanked by heterologous amino acid sequences at both termini.

Contrary to the Examiners assertion, these results do not prove that N-terminus cleavage does not take place, instead they show that when the BIL domain is flanked by heterologous sequences on both ends, processing results in either both N- and C-terminal cleavage or just C-terminal cleavage. Thus, N-terminal cleavage does take place, but when accompanied by C-terminal cleavage it typically results in splicing. This may be due to the sequence of cleavage events and thus does not imply that when flanked by an N-terminal sequence only, BIL domain auto-processing could not result in N-terminal cleavage and release of the N-terminus flanking sequence.

Indeed the results presented in Example 3 of the instant application clearly demonstrate that BIL domains are also capable of independent N-terminus cleavage. This Example clearly states that:

> "The *in-vivo* expressed MBP-4825rhosp-CBD chimera was shown to display N-terminal auto-cleavage activity via chitin or amylose based affinity purification of expressed protein and electrophoretic separation, and Coomassie blue staining of electrophoretically separated protein (Figure 11a)" (Emphasis added).

Thus, the instant specification provides the enablement necessary for an autoprocessing segment that is attached at an N- and/or a C- terminus thereof to a heterologous amino acid sequence.

The Examiner also states that the specification teaches that for cleavage to take place a nucleophilic group has to be present in the amino acid terminus of the polypeptide next to the C-terminus of the auto-processing segment.

As is clearly shown in the Example section of the instant application, SEQ ID NO:31 as well as other BIL sequences were effective in processing non-modified protein sequences flanking such auto-processing segments. In fact, the instant specification repeatedly states that the auto-processing segments of the present invention include the sequence information necessary for auto-processing and that unlike intein domains, the segments of the present invention are also capable of

processing without a need for stringent requirements in flanking sequences. Thus, the auto-cleavage capability of the presently claimed chimeric polypeptide is embodied by SEQ ID NO: 31 and therefore no additional sequence limitations are necessary for effective auto-processing of the chimeric polypeptide.

With respect to claims 16-18, clearly, such affinity tags are well known in the art and are routinely used for purification of cells, viruses, molecules and the like. The present invention does not teach or suggest novel affinity tags but rather generally mentions use of affinity tags in certain embodiments. It stands to reason that one of ordinary skill in the art would be more than capable of identifying and selecting suitable tags which can be incorporated into the present invention and utilized in purification of cells and viruses.

In addition, the instant specification provides several specific examples of suitable affinity tags including "streptavidin, His-tags, strep-tags, epitope tags, maltose-binding proteins, and chitin-binding domains."

Claims 14, and 16-17 have now been amended to more accurately define the affinity tags.

Thus, in view of the arguments presented above and the claim amendments entered herewith, Applicant strongly believes that the instant specification provides the enablement necessary for making and using the present invention as now claimed.

35 U.S.C. § 112, Second Paragraph Rejections

The Examiner has rejected claims 1-18 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 5, the Examiner states that the recitation "... said auto-cleavage" lacks antecedent basis. Claim 5, as well as claims 6, 11 and 13 have now been amended to replace the term "auto-cleavage" with the term "autoprocessing" described in claim 1. In addition, claims 5 and 6 have now been amended to more

clearly define the arrangement of the chimeric polypeptide and the product resultant from autoprocessing.

35 U.S.C. § 102 Rejections

The Examiner has rejected claims 1-12 and 15-17 under 35 U.S.C. 102(b) as being anticipated by Chong et al.

Applicant has now amended claim 1 to more clearly define the subject of the invention. As suggested by the Examiner, claim 1 now recites "the autoprocessing segment having the amino acid sequence set forth by SEQ ID NO: 31" thereby defining the autoprocessing segment as that including the entire sequence set forth in SEQ ID NO:31.

35 U.S.C. § 103 Rejections

The Examiner has rejected claims 1-17 under 35 U.S.C. 103(a) as being unpatentable over Chong et al. (1996).

The Examiner has also rejected claims 16 and 18 under 35 U.S.C. 103(a) as being unpatentable over Chong et al. (1996) as applied to claims 1-12 and 14-17 in view of Jarvik et al.

The Examiner has also rejected claims 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Chong et al. (1996) as applied to claims 1-12 and 14-17 in view of Chong et al. (1998).

Claim 1 has now been amended as described above with respect to the 102 rejection.

In addition, it should be noted that although the BIL domains of the present invention are somewhat similar in function to previously known intein domains (such as those described by Chong et al.), they are structurally distinct therefrom, as is clearly described in the Examples section of the instant application:

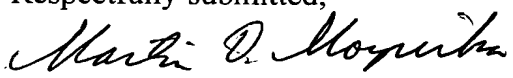
> "Both Type A and Type B BIL domains were found to be distinct from inteins in having additional unique sequence

> motifs, in not being integrated in highly conserved sites of essential proteins, and in not comprising endonuclease domains."

In light of the amendments to claim 1 and the clear structural and functional differences that exists between the autoprocessing domains of the present invention and those described by Chong, Applicant strongly believes that the present invention as claimed is patentable with respect to Chong et al.

In view of the above amendments and remarks it is respectfully submitted that claims 1, 5-18 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



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Enclosures:

- One month Extension Fee